

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A method of identifying an agent which modulates 2-oxoglutarate dependent oxygenase activity, the method comprising:
 - contacting a 2-oxoglutarate dependent oxygenase and a test agent in the presence of a substrate comprising one or more ankyrin ~~repeats repeat, or fragment thereof~~, in conditions under which the substrate is hydroxylated in the absence of the test agent; and
 - determining hydroxylation of the substratethereby determining whether or not the agent modulates 2-oxoglutarate dependent oxygenase activity.
2. (Original) A method according to claim 1, wherein the substrate is hydroxylated at an asparagine residue.
3. (Original) A method according to claim 2, wherein the asparagine residue is part of a valine-asparagine, aspartate-valine-asparagine, isoleucine-asparagine or leucine-asparagine sequence.
4. (Currently amended) A method according to claim 1, wherein the substrate is I κ B- α , p105, FEM-1, p19-INK-4d, GABPbeta, Tankyrase 1/2, 2-5 A(adenine)-dependent RNase (2-5A-d-R), Gankyrin, Myotrophin, M110, FGIF (Factor Inducing Foetal Globin), or a fragment of any thereof.
5. (Original) A method according to claim 4, wherein the substrate is p105 or a fragment thereof comprising Asn 778 of p105 or a peptide analogue of p105 or fragment thereof comprising an asparagine equivalent to Asn 778 of p105 and wherein hydroxylation of Asn 778 or of a said equivalent asparagine is determined.
6. (Previously presented) A method according to claim 1, wherein the 2-oxoglutarate dependent oxygenase is a JmjC protein.

7. (Original) A method according to claim 6, wherein the JmjC protein is factor inhibiting hypoxia-inducible factor (FIH).

8. (Previously presented) A method according to claim 1, wherein the hydroxylation of the substrate is determined by monitoring 2-oxoglutarate turnover.

9. (Previously presented) A method according to claim 1, wherein the hydroxylation of the substrate is determined by mass spectrometry.

10. (Previously presented) A method according to claim 1, wherein the hydroxylation of the substrate is determined by monitoring for transcription or expression of a reporter gene driven by a promoter regulated by an ankyrin repeat protein.

11. (Previously presented) A method according to claim 1 further comprising formulating an agent identified as a modulator of 2-oxoglutarate dependent oxygenase activity with a pharmaceutically acceptable recipient.

12. (Currently amended) A method of identifying an agent which selectively modulates activity of a first 2-oxoglutarate dependent oxygenase, the method comprising:

(a)(i) contacting a first 2-oxoglutarate dependent oxygenase and a test agent in the presence of a substrate comprising one or more ankyrin ~~repeats repeat, or fragment thereof~~, in conditions under which the substrate is hydroxylated in the absence of the test agent; and

(ii) determining hydroxylation of the substrate;

(b)(i) contacting a second 2-oxoglutarate dependent oxygenase and a test agent in the presence of a substrate comprising one or more ankyrin ~~repeats repeat, or fragment thereof~~, in conditions under which the substrate is hydroxylated in the absence of the test agent; and

(ii) determining hydroxylation of the substrate;

thereby determining whether or not the agent selectively modulates activity of the first 2-oxoglutarate dependent oxygenase.

13. (Original) A method according to claim 12, wherein the test agent inhibits activity of the first 2-oxoglutarate dependent oxygenase.

14. (Currently amended) A method according to claim 12, wherein the first 2-oxoglutarate dependent oxygenase is factor inhibiting hypoxia-inducible factor (FIH).

15. (Currently amended) A method according to claim 12, wherein the second 2-oxoglutarate dependent oxygenase is a prolyl hydroxylase domain (PHD).

16. (Previously presented) A method according to claim 12, wherein the first 2-oxoglutarate dependent oxygenase is a PHD.

17. (Previously presented) A method according to claim 16, wherein the second 2-oxoglutarate dependent oxygenase is FIH.

18. (Previously presented) A method according to claim 12, wherein the substrate is hydroxylated at an asparagine residue.

19. (Currently amended) A method of identifying an agent which selectively modulates 2-oxoglutarate dependent oxygenase activity on a first substrate, the method comprising:

(a)(i) contacting a 2-oxoglutarate dependent oxygenase and a test agent in the presence of a first substrate, ~~or fragment thereof~~, in conditions under which the substrate is hydroxylated in the absence of the test agent; and

(ii) determining hydroxylation of the first substrate; and

(b)(i) contacting a 2-oxoglutarate dependent oxygenase and a test agent in the presence of a second substrate, ~~or fragment thereof~~, in conditions under which the substrate is hydroxylated in the absence of the test agent; and

(ii) determining hydroxylation of the second substrate;

wherein at least one of said first and second substrates comprises one or more ankyrin ~~repeats~~ ~~repeat~~;

thereby determining whether or not the agent selectively modulates 2-oxoglutarate dependent oxygenase activity on a first substrate.

20. (Currently amended) A method according to claim 19, wherein the first and/or second substrate comprising one or more ankyrin ~~repeats~~ ~~repeat~~ is hydroxylated at an asparagine residue.

21. (Currently amended) A method according to claim 19, wherein the first substrate is HIF and the second substrate comprises one or more ankyrin ~~repeats~~ ~~repeat~~.

22. (Currently amended) A method according to claim 19, wherein the second substrate is HIF and the first substrate comprises one or more ankyrin ~~repeats~~ ~~repeat~~.

23. (Currently amended) A method according to claim 19, wherein the first and second substrates are different and each comprises one or more ankyrin ~~repeats~~ ~~repeat~~.

24. (Previously presented) A method according to claim 19, wherein the 2-oxoglutarate oxygenase is a Jmjc protein.

25. (Previously presented) A method according to claim 1, wherein the test agent is a polypeptide comprising an ankyrin repeat or an analogue thereof.

26. (Original) A method according to claim 25, wherein the analogue is an ankyrin repeat that lacks an asparagine residue capable of being hydroxylated by 2-oxoglutarate dependent oxygenase.

27-38. (Cancelled).